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## Original Research

## Adjuvant chemoradiotherapy in pancreatic adenocarcinoma—Are we forcing a milestone?

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## ABSTRACT

Survival for pancreatic ductal adenocarcinoma is low and the role of adjuvant therapy remains controversial, with the European studies indicating survival benefit of chemotherapy over chemoradiation, whereas the American reports indicate an undoubted benefit with chemoradiation. Whatever is the mode of adjuvant care, two things are obvious in the management of this disease: surgery is the mainstay of treatment and a complete resection is the only hope of cure. Secondly, irrespective of the adjuvant treatment modality, survival advantage is limited and five-year survival has failed to reach that of other malignancies. The mixed results obtained from the various adjuvant therapy trials indicate that a uniform protocol is yet to be reached. A milestone is said to have been reached when a treatment or a treatment modality revolutionizes the outcome of a disease. As of now the adjuvant treatment in pancreatic adenocarcinoma is still evolving. Maybe a fresh look is needed at the biological aspect of the disease to add a new thought in its management, as has happened with other human malignancies.

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Despite the progress made in terms of aggressive loco-regional therapy, survival data in pancreatic adenocarcinoma have not significantly improved in the last 25 years. The 5-year survival rate following complete resection is 25–30% for node-negative and 10% for node-positive cancers.<sup>1</sup> Complete surgical resection of the tumor remains the only chance of cure but a true radical surgery is actually achievable in less than 20% of cases.<sup>2</sup> The high risk of local and systemic recurrence as well as an overall poor survival is the rationale for the use of adjuvant therapy in this cancer.

In the late 1970s and early 1980s, a trial conducted by the Gastrointestinal Tumor Study Group (GITSG) demonstrated a definite survival advantage with adjuvant chemoradiotherapy (CRT) in patients with resected pancreatic cancer.<sup>3</sup> Unfortunately, the study population was too small ( $n = 43$ ) for any convincing conclusion and it was unclear whether the survival advantage was due to the combination of CRT and maintenance chemotherapy or to any one of these. This was followed by a major trial by the Johns Hopkins Hospital group<sup>4</sup> in which the outcome of patients undergoing resection only for pancreatic adenocarcinoma was compared with those who were offered adjuvant CRT following surgery. The study concluded that addition of adjuvant CRT significantly improved survival after pancreaticoduodenectomy (19.5 versus 13.5 months).

Subsequently two large-scale randomized controlled trials (RCTs) in Europe however failed to confirm a significant benefit of adjuvant CRT over resection alone. The European Organization for Research and Treatment of Cancer (EORTC) study did not show any significant benefit of adjuvant CRT over surgery alone although a trend in favor of CRT was suggested.<sup>5</sup> There was no reduction of loco-regional recurrence in either group or the 2-year survival estimate was 10% higher in the chemoradiation group. It concluded no overall benefit of adjuvant CRT over surgery alone. Technically however, the study is considered flawed and underpowered. The second multicenter trial by the European Study Group for Pancreatic Cancer (ESPAC-1) suggested a detrimental effect on survival with adjuvant chemoradiotherapy but not with chemotherapy or surgery alone.<sup>6</sup> Those who received CRT had an estimated 5-year survival rate of 10% compared to 20% among those who did not and 21% among those who received chemotherapy as opposed to 8% among those who did not. The benefit achieved by the use of chemotherapy in the ESPAC-1 trial was in contrast to the results of 2 RCTs from Japan,<sup>7,8</sup> which did not suggest prolonged beneficial effect with 5-FU-based combinations. Interestingly, a meta-analysis of 5 RCTs of adjuvant therapy in pancreatic cancer reported a 25% significant reduction in death risk with chemotherapy as adjuvant treatment.<sup>9</sup> There was no significant difference in the 2- and 5-year survival between those who received CRT and those who did not. However CRT was more effective than chemotherapy in patients with positive resection margins. It concluded that chemotherapy

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and not CRT is an effective adjuvant treatment in pancreatic cancer. However very recently a large collaborative study from the Mayo Clinic and the Johns Hopkins hospital demonstrated a significant survival benefit in those receiving adjuvant CRT compared to surgery alone (21.1 versus 15.5 months). Compared to surgery alone, adjuvant CRT improved survival by 33% after stratification by age, margin, node and T-stage status. Overall survival at 2- and 5-years was also superior with adjuvant CRT.<sup>10</sup>

The mixed results with the use of 5-FU-based chemotherapy gave way to the introduction of gemcitabine in 1996 as a probable better adjuvant regimen. It was considered a major step in the adjuvant treatment of pancreatic cancer, which is still currently practiced as the standard of care. After an initial trial had demonstrated survival advantage with gemcitabine,<sup>11</sup> multicentric randomized trials like the CONKO-001<sup>12</sup> and RTOG-9704<sup>13</sup> followed. Gemcitabine was found to significantly delay the development of recurrent disease after complete resection of pancreatic cancer. Subgroup analyses also demonstrated a significant disease-free survival in patients with either R0 or R1 resection. It was found to be superior to 5-FU-based regimen in terms of improved survival.<sup>13</sup> The most recent ESPAC-3(v2) trial,<sup>14</sup> which recruited 1088 patients from 16 countries, demonstrated no significant difference between gemcitabine and 5-FU plus leucovorin on the treatment outcome and survival in patients who had undergone R0 or R1 resections for pancreatic cancers. Despite heterogeneity, subgroup analysis proved no significant difference in the effect of treatment according to the R-status.

Since surgical resection of localized disease remains the only hope for cure and since most of the pancreatic tumors are detected late, chance for a curative resection is available to a minor subset of patients with early detection. Moreover, even if it appears to be potentially curative on preoperative imaging, getting a reliable retroperitoneal margin may not always be feasible during surgery. In this setting, the option of neoadjuvant treatment has been considered to downstage the disease and to combine it with an oncological resection for better local control and survival. In a case control study, Ishikawa et al. in 1994<sup>15</sup> observed that downstaging of pancreatic cancers with neoadjuvant CRT allows oncological resection. In another trial by Evans et al., 28 patients with adenocarcinoma of the pancreatic head received preoperative chemoradiation and continuous infusion of 5-FU.<sup>16</sup> Four to five weeks later the patients were restaged. Of the 23 patients who underwent laparotomy, curative pancreaticoduodenectomy could be done in 17 patients. Hoffman et al.<sup>17</sup> recruited 53 patients who received preoperative continuous infusion 5-FU, mitomycin-C and radiation therapy. Out of 53 patients, 24 showed downstaging and underwent resection with a median survival of 15.7 months compared with 9.7 months for the entire group.

In response to the question of whether neoadjuvant CRT improved survival, only a few studies have shown high median survival rates of two years or more following neoadjuvant treatment. In a study by Snady et al.,<sup>18</sup> 68 patients received neoadjuvant treatment with concurrent split course EBRT and 5-FU, streptozotocin and cisplatin. Of these, 20 patients (29%) who underwent resection achieved a median survival rate of 32 months as compared to 23.6 months for the entire group. Mehta et al.<sup>19</sup> reported a median survival of 30 months with neoadjuvant treatment but only in nine patients. Pisters et al.<sup>20</sup> used preoperative rapid fractionation chemoradiation with 5-FU for 2 weeks and concurrent external beam radiation therapy (EBRT) with 30 Gy for 2 weeks in 35 patients. Following resection, the patients received intraoperative radiation therapy (IORT). The median survival rate was 25 months and the 3-year actuarial overall survival rate was 23%. In another study,<sup>21</sup> a median survival of 25 months was observed in the resected group (21 of 34 patients) following neoadjuvant twice-weekly gemcitabine (50 mg/m<sup>2</sup>) and EBRT (50.4 Gy) in locally advanced potentially resectable pancreatic

cancers. Calvo et al.<sup>22</sup> evaluated neoadjuvant tegafur (1200 mg/day) with concurrent EBRT in potentially resectable pancreatic cancers in 15 patients and concluded that median survival was significantly better in the resected group compared to those not undergoing resection (23 versus 8 months). Unfortunately the benefits of neoadjuvant CRT in improving median survival have been reported mostly from small, single institution-based studies most of which are non-randomized and contain a heterogeneous disease population.

Preoperative chemoradiation for potentially resectable pancreatic cancer has several advantages. It eliminates the delay of adjuvant treatment from postoperative recovery and could spare unnecessary surgery for patients with metastatic disease evident on restaging after neoadjuvant therapy. During neoadjuvant therapy, disease progression occurs in 15–25% of the patients, with the appearance of liver metastases and/or peritoneal carcinosis.<sup>23</sup> Downstaging after neoadjuvant treatment may theoretically increase the likelihood of a negative surgical margin. It could prevent tumor cell implantation and dissemination during surgery but this has not been proven. In recent controlled clinical trials comparing historical and prospective control groups, the frequency of downstaging was observed to be between 13% and 45%.<sup>23</sup> Neoadjuvant chemoradiation resulted in a decrease in the frequency of cancer-positive margins and oncological resection after neoadjuvant chemoradiation resulted in a median survival between 15 and 32 months. Moreover after neoadjuvant treatment no increase in postoperative complications has been reported. Unfortunately, many reports of neoadjuvant therapy for pancreatic cancer have included heterogeneous patient populations, enrolling patients with resectable, marginally resectable and locally advanced pancreatic cancer.<sup>17,19,21,24–26</sup> This confounds reports of resection rates and complicates comparison with other studies.

In the case of locally advanced pancreatic cancer, the aim of preoperative chemoradiation has been to downstage the loco-regional disease and to facilitate surgical resection, importantly R0 resection. Locally advanced pancreatic cancer describes pancreatic cancer without evidence of distant metastasis but locally unresectable due to tumor encasement of major vessels such as celiac and superior mesenteric arteries or the portal vein. Downstaging in this group of locally advanced pancreatic cancer leads to a separation between tumor and vessel wall and to an increase of resection rates between 29% and 80%, and a survival benefit after oncological resection.<sup>23</sup> Although local control rates have been improved by radiation therapy, systemic failure remains a major obstacle in improving the long-term survival. Due to high rates of distant metastasis and poor overall survival rates, the value of secondary resection after conversion of unresectable disease to resectable disease is questioned in the treatment of this subgroup. Since this issue has not been addressed in larger studies, the question remains controversial. The available smaller phase I and II studies report an increase in the median survival following secondary resection compared to all patients. But as these are small and single institution-based studies, selection bias cannot be ruled out. Further, interpretation of these data is difficult because of different criteria for resectability. A specialist pancreatic cancer surgery team can often resect what is considered by another team to be unresectable locally advanced disease, indicating that primary resectability may have been defined differently.<sup>27</sup> In cases where no downstaging with secondary resectability can be achieved, median survival is only around 10 months and 5-year survival is near zero. However, in this subset of patients significant palliative benefit can be achieved by CRT. Complete pain relief can be obtained in as many as 50–80% of patients, as well as some improvement in wasting, obstructive symptoms, performance status, and anorexia.<sup>28</sup>

As early as in 1983, it was thought that adding IORT to the protocol to deliver much higher doses of radiation to the

conventional EBRT will lead to better local control. The feasibility of this technique was demonstrated on a patient with locally advanced pancreatic cancer, who survived disease-free for more than 19 months after total pancreatectomy with portal resection followed by IORT to the tumor bed and regional lymph nodes.<sup>29</sup> A subsequent RCT, which compared the outcome of IORT (20 Gy) or observation or EBRT (50 Gy) showed significant improvement of local control and a better overall survival rate in the IORT group (18 versus 12 months). Despite this improvement in loco-regional control, no difference in the disease-free survival was observed.<sup>30</sup> Several other studies have described favorable effects of IORT in pancreatic cancer,<sup>31–33</sup> but are limited with regard to any clear recommendation. It has also been suggested that neoadjuvant CRT may actually improve the effects of IORT in terms of local control and overall survival.<sup>34,35</sup> While metastasis still remains the main challenge for this disease, the improvement of local control by adding IORT may have an impact on the survival of patients due to a lesser tendency for disease spread. Clearly, a more efficient multimodality treatment strategy is needed to control micrometastasis and to select patients who could benefit by surgery and local therapies.

The treatment of pancreatic adenocarcinoma has witnessed the use of different chemotherapy regimens, chemotherapy alone or in combination with radiotherapy in different doses, techniques of delivery and sequence of usage. Overall, these treatments are still evolving. Although adjuvant chemoradiation has achieved local control in mixed reports, long-term survival advantage has eluded the clinician for the past three decades. The benefit has been only in statistical terms, and the 5-year survival rate still remains dismally low. This, coupled with the morbidity of surgery and chemoradiation, raises the important question of whether or not we have reached a milestone in the treatment of this disease. Perhaps a shift of focus is needed toward the biological behavior of the disease utilizing a better understanding of tumor biology with regard to cellular/genetic function coupled to a strategic implementation of existing therapeutic protocols in the future.

#### Conflict of interest

None.

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